REMARKS/ARGUMENTS

Reconsideration and allowance of the present application based on the following remarks are respectfully requested.

Upon entry of the above amendments, claims 1-14 will be pending in the application.

The specification on pages 2 and 3 is amended to conform the designations for X^1 in the text and in the formula. Similar changes are made in the claims and in the Abstract.

Claim 1 is re-written to recite the reaction of the compound of formula (2) with the compound of formula Al(OR)₃ at the beginning of the claim to precede the definitions of the various substituents. Claim 3 is similarly re-written.

Claims 1 and 3 are also amended to define the substituents for R as being one or more of halogen or amino substituents. Support for this amendment is found on page 3, lines 1-3.

Claims 1 and 2 are amended to define the base B as a nucleobase (see, e.g., page 3, line 19).

The dependencies of claims 5 and 8 have been corrected to avoid the improper multiple claim dependencies.

Claim 7 is amended to be directed to the embodiment of steps a) and b) while new claim 9 is directed to the embodiment formerly represented by steps c) and d) of claim 7.

Claims 10-11 are directed to embodiments wherein the groups X and X^1 represent H or wherein at least one of the groups X and X^1 represent a protecting group. Claim 12 recites representative examples of classes of protecting groups (*see*, e.g., page 3, lines 4-12).

Claims 13 and 14 are directed to particular embodiments of the leaving group L as described on page 4, lines 4-11.

Accordingly, no new matter is added.

The acknowledgements of the receipt of the certified copies of the priority documents and the cross-reference made by the Preliminary Amendment are appreciated.

The claim objection for claims 7 and 8 is obviated by the present claim amendments. No pending claim is improperly multiply dependent.

The rejection of claims 1 and 2, under 35 U.S.C. § 112, first paragraph, is respectfully traversed for at least the following reasons.

The assertion that these claims are not enabled by the specification is believed to be in error. First, the pending claims now define the base B as a nucleobase.

Second, while there may not have been presented examples wherein, for example, the nucleobase is a purine, the fact remains that the disclosure is enabling and that the Examiner has not presented any objective basis for doubting that the process would not proceed via the indicated reaction mechanism for any of the nucleobases. The specification provides guidance for selecting nucleobases and for carrying out the desired reaction for preparing 2' derivatized nucleosides wherein B may be any nucleobase. In each case, the process involves the displacement of a leaving group by aluminum alkoxide. There is no objective reason to doubt that any leaving group, including a nucleobase leaving group, would not also be displaced by an OR group from Al(OR)₃.

In this case, it does not appear to be questioned that the starting reactants (e.g.,, compound of Formula (2) and Al(OH)₃) are enabled by the specification or that the reaction conditions for carrying out the claimed process (see, e.g.,, page 5, lines 7-26 and examples) are not adequately set forth. Given this information, it would not entail undue experimentation to ascertain the specific conditions for any particular nucleobase B, within the disclosed parameters, for carrying out the claimed process to prepare the compound of Formula (1).

The suggestion that undue experimentation would be required to determine which base, other than pyrimidine, would be able to chemically bond to the 2'-position to form a leaving group, as per claim 2, does not explain why undue experimentation would be required, much less why there is an objective basis for doubting that other nucleobases could be so used, notwithstanding that only pyrimidine nucleosides were assessed. The disclosure does set forth other nucleobases and the use of such other nucleobases and the determination of the ability to function as a leaving group would be routine without requiring undue experimentation.

Accordingly, it is respectfully submitted that claims 1 and 2 are enabled by the application as filed and reconsideration and withdrawal of this rejection is respectfully requested.

New claim 13 is directed to the embodiment wherein the leaving group is one of the groups other than the base B. Claim 14 is directed to the embodiment wherein the leaving group is a pyrimidine.

Reconsideration and withdrawal of the rejection of claims 1-8, under 35 U.S.C. § 112, second paragraph, is respectfully requested for at least the following reasons.

The rejection first questions the definiteness of the term "protecting group."

Applicants respectfully disagree. The term "protecting group" is well understood in the field of organic chemistry, in general, and in nucleotide chemistry, in particular. The protection of an otherwise reactive position in nucleotide chemistry is well documented and the specification provides ample disclosure of representative protecting groups (*see*, *e.g.*, page 3, lines 4-18, as well as representative techniques for removing the protecting groups (*see*, *e.g.*, page 6, lines 4-22). A search of the PTO's patent database, under the search terms "protecting group" (in the Claims field) and "nucleoside" (anywhere in the text) had 554 hits (database 1974 to present), clearly evidencing that those skilled in the art understand the metes and bounds of the term "protecting group" in this area of technology.

The alleged indefiniteness of the term "base" is without foundation since the practitioner of ordinary skill would have no difficulty in ascertaining the meaning of the term "base." In any case, the claims are amended to even further clarify base as "nucleobase" which has a well understood meaning.

The term "optionally substituted" is also not indefinite. The phrase means that the R group may be one of the specified groups and these groups may be unsubstituted or substituted. Again, however, the claims are amended to more particularly define optional substituents.

The term "substantially anhydrous conditions" is not indefinite and the meaning and scope thereof would be readily understood by the practitioner of ordinary skill in the art. For example, since the involved reaction is a nucleophilic displacement reaction, the practitioner would readily understand that water is a competing nucleophile and, therefore, its presence is generally undesirable. The practitioner would also know that water is able to hydrolyze compounds of formula Al(OH)₃, therefore, would carry out the reaction in the absence of water to the extent reasonable. However, since it is further recognized that it may not be generally or reasonably possible to maintain the complete absence of water, the practitioner would understand that the reaction should be carried out under conditions where the concentration of water is such that it would not materially affect the effectiveness of the Al(OR)₃ derivatization process. The amounts of water which would not materially adversely

effect the derivatization process are well known to those of ordinary skill in the general field of organic chemistry in relation to both nucleophilic displacement and Al(OH)₃ hydrolysis.

Furthermore, the examples in the specification do describe typical methods of removing water (such as, e.g., use of sodium wire or calcium hydride) (see, e.g., page 6, line 35 to page 7, line 2). Those skilled in the art would recognize that such methods do not achieve 100% water removal but, rather, adequately exemplify "substantially anhydrous conditions."

Finally, as noted above, claims 1 and 3 are re-written to avoid the use of the term "above" in reference to the location of a definition.

Therefore, for at least the above reasons, the rejection of claims 1-8, under the first paragraph of 35 U.S.C. § 112, should be withdrawn.

Reconsideration and withdrawal of the rejection, as applied to examined claims 1-6, under 35 U.S.C. § 103(a), as unpatentable over WO 96/27606 (ISIS) in view of McGee, *et al.* (McGee), is respectfully requested for at least the following reasons.

ISIS relates to a process for synthesizing 2'-O-substituted pyrimidine nucleosides by a process which features alkylation of a 2,2'-anhydropyrimidine nucleoside or a 2S,2'-anhydropyrimidine nucleoside with a weak nucleophile (alcohol) in the presence of a Lewis acid (trialkyl borate). There is no disclosure of using Al(OH)₃ as the Lewis acid and only the borates are mentioned in any specificity and in the examples.

The disclosure on page 33 provides a general definition of Lewis acid of which di and tri valent hard acids are preferred and borates, particularly trialkyl borates, are especially preferred. There is also a disclosure of at lines 18-25 that di and tri valent cations of di and tri valent metals and their complexes are known as Lewis acids. Fourteen (14) different metals are mentioned and six (6) different classes of complexes are mentioned, with no directions or guidelines for selecting any combination of a particular metal with a particular complex. Therefore, there is nothing in this disclosure which would lead the practitioner to Al(OH)₃ or any other particular Lewis acid, other than the borates.

The disclosure of McGee does not provide any motivation to pick and choose Al(OH)₃ from among any of the non-preferred Lewis acids or to select any of these aluminum compounds for reaction with a compound of Formula (1) or Formula (3).

The disclosure of McGee is specifically limited to <u>divalent</u> metal alkoxides. Therefore, the practitioner, reviewing the disclosure of McGee - even if motivation is provided for using other than ISIS' preferred borate Lewis acids - would only be motivated to consider the divalent metal compounds and not the trivalent metal compounds, such as, for example, Al(OR)₃.

Therefore, it is respectfully submitted that the embodiments of the invention, as set forth in the rejected claims 1-6, or the unexamined claims 7 and 8, or any of the new claims 9-14, would not have been *prima facie* obvious over ISIS in view of McGee.

While, for the reasons submitted above, the present claims would not have been *prima* facie obvious, it is further noted that the embodiments of Applicants' invention, as currently claimed, provide unexpectedly effective performance by using aluminum trialkoxides.

Such unexpectedly good performance is demonstrated by the examples and comparative examples in the specification. In particular, reference is made to the examples for the preparation of 2'-O-(2-methoxyethyl)uridine (page 7, lines 15-25) wherein the yield of the title compound was ca. 91% for the reaction at 125 °C (the boiling point of 2-methoxyethanol). In contrast, in the disclosure of ISIS, example 41, pages 54-55, which used tris(2-methoxy ethyl) borate, the yield was only 63%, and this under more forceful conditions of temperature from 155 °C to 160 °C.

When these results are further viewed in light of the disclosure by McGee, wherein it is shown that larger alcohols give much lower yields (*see*, *e.g.*, the results for examples 3b, 3c and 3d - lower yields for allyl, ethyl and propyl compared to methyl), the improved results according to the present invention are even more surprising.

Therefore, even if there is considered to be a *prima facie* case for obviousness, the invention, considered as a whole, including the improved results, would not have been obvious to the person of ordinary skill in the art.

Therefore, all objections and rejections having been addressed, it is respectfully submitted that the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Should any issues remain unresolved, the Examiner is encouraged to contact the undersigned attorney for Applicants at the telephone number indicated below in order to expeditiously resolve any remaining issues.

Respectfully submitted,

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Attachment: Information Disclosure Statement